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Regression of Diffuse Ventricular Fibrosis Following Restoration of Sinus Rhythm With Catheter Ablation in Patients With Atrial Fibrillation and Systolic Dysfunction

A Substudy of the CAMERA MRI Trial

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ABSTRACT

OBJECTIVES This study sought to determine if diffuse ventricular fibrosis improves in patients with atrial fibrillation (AF)-mediated cardiomyopathy following the restoration of sinus rhythm.

BACKGROUND AF coexists in 30% of heart failure (HF) patients and may be an underrecognized reversible cause of left ventricular systolic dysfunction. Myocardial fibrosis is the hallmark of adverse cardiac remodeling in HF, yet its reversibility is unclear.

METHODS Patients with persistent AF and an idiopathic cardiomyopathy (left ventricular ejection fraction [LVEF] ≤45%) were randomized to catheter ablation (CA) or ongoing medical rate control as a pre-specified substudy of the CAMERA-MRI (Catheter Ablation versus Medical Rate Control in Atrial Fibrillation and Systolic Dysfunction—an MRI-Guided Multi-centre Randomised Controlled Trial) trial. All patients had cardiac magnetic resonance imaging scans (including myocardial T1 time), serum B-type natriuretic peptide, 6-min walk tests, and Short Form-36 questionnaires performed at baseline and 6 months. Sixteen patients with no history of AF or left ventricular systolic dysfunction were enrolled as normal controls for T1 time.

RESULTS Thirty-six patients (18 in each treatment arm) were included in this substudy. Demographics, comorbidities, and myocardial T1 times were well matched at baseline. At 6 months, patients in the CA group had a significant reduction in myocardial T1 time from baseline compared with the medical rate control group (−124 ms; 95% confidence interval [CI]: −23 to −225 ms; $p = 0.0176$), although it remained higher than that of normal controls at 6 months ($p = 0.0017$). Improvements in myocardial T1 time with CA were associated with significant improvements in absolute LVEF (+12.5%; 95% CI: 5.9% to 19.0%; $p = 0.0004$), left ventricular end-systolic volume ($p = 0.0019$), and serum B-type natriuretic peptide (−216 ng/l; 95% CI: −23 to −225 ng/l; $p = 0.0125$).

CONCLUSIONS The improvement in LVEF and reverse ventricular remodeling following successful CA of AF-mediated cardiomyopathy is accompanied by a regression of diffuse fibrosis. This suggests timely treatment of arrhythmia-mediated cardiomyopathy may minimize irreversible ventricular remodeling. (J Am Coll Cardiol EP 2018;4:999-1007) © 2018 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

6MWT = 6-min walk test

AF = atrial fibrillation

BNP = brain natriuretic peptide

CA = catheter ablation

CMR = cardiac magnetic resonance imaging

LGE = late gadolinium enhancement

LV = left ventricular

LVEF = left ventricular ejection fraction

MRC = medical rate control

MRI = magnetic resonance imaging

SF-36 = 36-Item Short Form Survey

Myocardial fibrosis is the hallmark of many cardiac diseases (1,2), including systolic heart failure (3) and atrial fibrillation (AF) (4,5), and is the end result of myriad adverse remodeling processes. AF is a well-described cause of systolic dysfunction in selected patients. Catheter ablation (CA) for AF in heart failure is associated with a reduction in mortality and heart failure hospitalization (6,7). In CAMERA-MRI (Catheter Ablation versus Medical Rate Control in Atrial Fibrillation and Systolic Dysfunction—an MRI-Guided Multi-centre Randomised Controlled Trial) study, patients with AF and unexplained left ventricular (LV) systolic dysfunction randomized to CA demonstrated significant improvements in LV systolic dysfunction compared with medical rate control (MRC) (8,9). The improvement in LV ejection fraction (LVEF) following the restoration of sinus rhythm with CA was greater in the absence of ventricular late gadolinium enhancement (LGE) on cardiac magnetic resonance imaging (MRI) scans. The extent of

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myocardial fibrosis has been associated with adverse outcomes in both AF and idiopathic cardiomyopathy (10). Diffuse or interstitial fibrosis can be detected by T1 mapping on cardiac MRI (3) scans and may be a precursor to more irreversible forms of replacement fibrosis (11). The reversibility of systolic impairment in this population affords a unique opportunity to examine the impact upon diffuse fibrosis in idiopathic cardiomyopathy. The extent, or otherwise, that diffuse fibrosis in heart failure is capable of regression with any form of therapy, is unclear. This study aimed to determine the impact upon diffuse ventricular fibrosis of recovery of systolic function following CA in AF-mediated cardiomyopathy compared with those with ongoing rate-controlled AF in a randomized controlled trial.

METHODS

STUDY DESIGN. This was a pre-specified secondary analysis of patients enrolled in CAMERA-MRI (8). Ethics committee approval was obtained at each participating center.

STUDY POPULATION. The inclusion criteria were as previously published (8). In summary: 1) age 18 to 85 years; 2) New York Heart Association functional class ≥II; 3) persistent AF; 4) LVEF ≤45% on baseline cardiac magnetic resonance (CMR) imaging; 5) significant coronary artery disease excluded via conventional or computed tomography-guided angiography or functional imaging; and 6) no other identifiable cause explaining LV systolic dysfunction. Patients were excluded if they: 1) were unable or unwilling to consent or commit to follow-up requirements; 2) had any contraindication to AF ablation; 3) had any contraindication to cardiac MRI; or 4) had paroxysmal AF. An additional 16 age-matched patients with no evidence of AF, structural heart disease, or heart failure underwent CMR scanning with native T1 mapping as normal controls. All participants provided written informed consent to participate in the study.

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PROCEDURES. Patients meeting the inclusion criteria underwent baseline echocardiography, 24-h Holter monitoring, 6-min walk test (6MWT), 36-Item Short Form Survey (SF-36), serum brain natriuretic peptide (BNP), and clinical review. 6MWT, SF-36, and clinical review were repeated at 3 and 6 months, and CMR, BNP, and echocardiography at 6 months.

CARDIAC MRI. Before CMR, rate control was optimized aiming for an average ventricular rate <100 beats/min on 24-h Holter monitoring. Baseline and 6-month CMR was performed by using a clinical 1.5-T MRI scanner (Signa HD 1.5-T, GE Healthcare, Waukesha, Wisconsin). Sequences were acquired during breath-holds of 10 to 15 s. Initial cine CMR sequences were performed in 3 standard long-axis (4-, 3-, and 2-chamber views) and short-axis (basal, mid, and apical) slices, kept identical for each subsequent sequence throughout the CMR examination. To calculate LV volume and function, a contiguous short-axis steady-state free precession stack was acquired (8-mm-thick slice, no gap), extending from the mitral valve annulus to the LV apex. LGE was obtained in both long- and short-axis views 10 min after a bolus (0.2 mmol/kg body weight to a maximum of 20 mmol) of gadolinium-diethylenetriamine pentaacetic acid (Magnevist, Schering, Germany) to identify regional fibrosis by using a T1-weighted inversion-recovery gradient echo technique. LGE was defined quantitatively by manually contouring regions of increased signal intensity consistent with scar using commercially available software (CVI42, Circle Cardiovascular Imaging, Inc., Calgary, Canada). For the purposes of this analysis, LGE negative was defined as <1% LGE present in the myocardium.

T1 MAPPING TECHNIQUE. Myocardial T1 times were estimated of by means of a prototype $SMART_1$ MAP sequence (Global Applied Science Laboratory, GE Healthcare). Each sequence was acquired within an end-expiration breath-hold using an electrocardiogram-triggered single-shot acquisition with a balanced steady-state free precession readout in a single mid- to short-axis slice. A series of images at the mid-LV short-axis level were acquired sequentially at increasing inversion times, pre-contrast (for non-contrast myocardial T1 time; inversion time [TI] range, 75 to 2,000 ms) during a single breath hold. After image acquisition, the short-axis images of varying TIs were transferred to an external computer for analysis using a dedicated research software package with a curve-fitting technique to generate T1 maps (cvi42, Circle Cardiovascular Imaging). T1 measurements were taken at the mid- to short-axis level by taking a region within the septum as has previously been described (12) and away from magnetic field distortions created by susceptibility effects. Additionally, we chose to measure T1 times in the mid-septum to avoid the risk of partial voluming resulting from variable triggering in AF, and thus we excluded participants whose susceptibility artifact involved the septum. Any mid-wall fibrosis (typical of dilated cardiomyopathy) was included, with the consideration that this represents a continuum with diffuse interstitial fibrosis (11,13). For each patient, T1 mapping data were independently assessed as being of sufficient quality (i.e., free from blood pool contamination and/or loop recorder artifact) in both the baseline and follow-up scans for that patient to be included in the analysis.

MRC. Patients randomized to ongoing rate control underwent 24-h Holter monitoring at 3 and 6 months following randomization, with medical therapy titrated to achieve a resting rate <80 beats/min, and average 24-h ventricular rate of <100 beats/min and post-exercise (6MWT) ventricular rate of <110 beats/min or maximal tolerated dose to achieve symptomatic control, in accordance with current guidelines (14).

CA PROCEDURE. CA was performed within 1 month of randomization as previously described (8). In brief, oral anticoagulation was discontinued 24 h pre-procedure with the exception of vitamin K antagonists or dabigatran, which was continued. All procedures were performed under general anesthesia with the assistance of a 3-dimensional mapping system (CARTO, Biosense Webster, Irvine, California) and image integration. After exclusion of intracardiac thrombus, decapolar and quadpolar catheters were positioned in the coronary sinus and His position, respectively. Transesophageal echocardiographic-guided double transseptal punctures were performed (BRK-1XS needle, SL1 8, 8.5-F sheaths). Unfractionated heparin was administered to achieve an activated clotting time of >350 s. Mapping of the left atrium and pulmonary veins was performed with a 20-pole circular mapping catheter, and ablation with a contact-force enabled 4-mm irrigated-tipped catheter (SmartTouch Thermacool, Biosense Webster) following electrical cardioversion to restore sinus rhythm (25 to 30 W). Pulmonary vein isolation was achieved with wide antral circumferential ablation with additional roof and inferior lines to achieve posterior left atrial wall isolation. Antiarrhythmic medication use post-ablation was at operator discretion.

AF MONITORING. In patients undergoing CA, AF recurrence was monitored via implantable loop recorder (CONFIRM, Abbott [Lake Bluff, Illinois], or REVEAL LINQ, Medtronic [Minneapolis, Minnesota]) implanted at the time of procedure. Recurrence was

TABLE 1 Participant Characteristics (N = 36)

	CA (n = 18)	MRC (n = 18)	p Value
Demographics			
Age (yrs)	59 ± 13	63 ± 7.1	0.26
CHA_2DS_2VASc score	2.6 ± 0.9	2.2 ± 1.1	0.20
Hypertension	44	22	0.36
Diabetes	17	28	0.73
Hyperlipidemia	33	17	0.51
BMI (kg/m^2)	31 ± 8.7	30 ± 2.7	0.42
Obstructive sleep apnea	28	11	0.45
Stroke/TIA	6	0	0.60
Medications			
ACE inhibitor or ARB	95	95	1.00
Cardioselective beta-blocker	89	95	0.55
Any beta-blocker	100	100	1.0
Spironolactone	33	61	0.10
Amiodarone	22	28	0.70
Antiarrhythmic therapy	28	28	1.00
Anticoagulation	100	100	1.00
AF history			
Mean duration of continuous AF (months)	24 ± 21	18 ± 13	0.27
Long-standing persistent AF	67	77	0.88
Previous electrical cardioversion	100	100	1.00
Resting HR (beats/min)	79 ± 9.4	76 ± 20	0.40
24-h average HR (beats/min)	87 ± 18	83 ± 19	0.35
Post 6MWT HR (beats/min)	95 ± 23	91 ± 19	0.57
Codiagnosis of AF and LVSD	78	61	0.75
Cardiac MRI findings			
LVEF	33 ± 8.0	36 ± 8.2	0.35
LGE	50	33	0.60
Average LGE	3.6 ± 7.8	2.2 ± 5.6	0.09
Native T1 relaxation time	1,285 ± 120	1,224 ± 125	0.14
LAVI (ml/m^2)	54 ± 16	53 ± 21	0.89
LVESV (ml/m^2)	80 ± 34	75 ± 29	0.62
LVEDV (ml/m^2)	118 ± 44	114 ± 36	0.79

Values are mean ± SD or %.

6MWT = 6-min walk test; ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARB = angiotensin receptor blocker; CA = catheter ablation; CHA_2DS_2VASc = age, sex, and history of congestive heart failure, hypertension, stroke/transient ischemic attack/thromboembolism, vascular disease, and diabetes; HR = heart rate; LAVI = left atrial volume index; LGE = late gadolinium enhancement; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; LVSD = left ventricular systolic dysfunction; MRC = medical rate control; MRI = magnetic resonance imaging; TIA = transient ischemic attack.

defined as documented AF or atrial tachycardia >30 s occurring beyond a 4-week blanking period post-procedure. Recorded rhythms were manually verified by study investigators during clinical assessments at 6 weeks, 3 months, and 6 months post-CA. AF burden was determined using manufacturers' automated algorithms and expressed as the percentage of total time in AF from time of implant.

STATISTICAL ANALYSIS. Data are expressed as mean ± SD unless otherwise indicated. Between-group comparisons were performed using Student's *t*-test for continuous variables or the chi-square test or Fisher's exact test for categorical variables. Within-group comparisons of continuous variables between baseline and follow-up were performed using a paired *t*-test. Confidence intervals for the difference of 2 independent proportions were calculated using Newcombe-Wilson score method (uncorrected) (15). McNemar's test was used for comparisons of proportions of paired samples. Analyses were conducted using SPSS software (version 24, IBM, Chicago, Illinois). The trial was registered with the Australia New Zealand Clinical Trials Registry (ACTRN12613000880741).

RESULTS

BASELINE CHARACTERISTICS. Of the 66 patients analyzed in the CAMERA-MRI study, 36 (18 in each arm) had both baseline and 6-month T1 mapping performed at CMR at baseline and 6 months has T1 data suitable for inclusion in this study. The baseline characteristics of included patients are shown in Table 1. Demographics, comorbidities, and risk factors were well matched between the groups. Baseline antifailure, antiarrhythmic drug therapy, and rate control (including resting, mean, and post-exercise) were also well established and well matched between the groups. In the MRC group, average ventricular rates at baseline (82 ± 19 beats/min) were maintained at 3 months (81 ± 14 beats/min) and at 6 months (79 ± 8.7 beats/min). There was no significant difference in LVEF or cardiac dimensions between the groups. At baseline, there was no significant difference in the myocardial T1 times between groups, although both groups had significantly higher values than normal controls (CA: $p < 0.001$; MRC: $p = 0.002$). LGE was present in 42% (15 patients) of patients with no difference between the groups ($p = 0.60$) (Table 1). The predominant pattern of fibrosis was midwall in 87% (n = 13) involving the septum (53%, n = 8), inferior wall (53%, n = 8), and the lateral wall (40%, n = 6). There were no crossovers between catheter ablation and MRC in this cohort.

PROCEDURAL CHARACTERISTICS AND AF OUTCOME. In those patients undergoing catheter ablation (n = 18), pulmonary vein isolation was achieved in all, with additional posterior wall isolation attempted in 94% (17) and achieved in 76% (13 of 17). Additional cavotricuspid isthmus ablation was performed in 11% (2). At 6 months, AF burden in the catheter ablation group was 0.8 ± 2.9%, with 89% (16) of patients with an AF burden <0.1%. Thirty-nine percent (n = 7) of patients undergoing CA continued or commenced antiarrhythmic drug therapy post-ablation. No patients underwent repeat catheter ablation during the 6-month

follow-up period. In the CA group, groin hematomas occurred in 2 patients, with 1 requiring blood transfusion and 1 developing pneumonia. There were no reported complications in the MRC group.

DIFFUSE VENTRICULAR FIBROSIS. At 6 months, there was a significant decrease in the myocardial T1 times in the CA group compared with the MRC group (−124 ms; 95% confidence interval: −23 to −225 ms; p = 0.017) with no significant difference at baseline (Tables 1 to 3, Figures 1 and 2). Although myocardial T1 times improved significantly in the catheter ablation group, they remained significantly higher compared with normal controls (1,192 ± 77.1 ms vs. 1,103 ± 71.8 ms; p = 0.0015) (Figure 2) at 6 months. Myocardial T1 times were higher in the MRC group compared with normal controls at baseline (p = 0.0017) and 6 months (p = 0.0024). Myocardial T1 times in patients with an absolute improvement in LVEF ≥15% from baseline decreased an average of −99 ± 159 ms compared with 2.0 ± 154 ms in those improving LVEF <15% (p = 0.09). In those undergoing CA, there was no difference in reduction in myocardial T1 times between those improving LVEF by ≥15% (−102 ± 167 ms) and those not (−83 ± 88 ms; p = 0.77). In the LGE-positive group, a significantly greater reduction in T1 time was demonstrated with CA compared with MRC (−145 ± 137 ms vs. +29 ± 185 ms; p = 0.05). In the LGE-negative group; there was no significant difference in change in T1 time (CA vs. MRC: −42 ± 117 ms vs. +31 ± 159 ms; p = 0.26).

REVERSE VENTRICULAR REMODELING. At 6 months, LVEF had significantly improved in the CA group compared with the MRC group (47 ± 11% vs. 37 ± 7.6%; p = 0.00377), with an absolute improvement in LVEF from baseline of +14 ± 11% vs. +1.5 ± 11% in MRC (p = 0.0004) (Tables 2 and 3). Six patients (33%) in the CA group had normalized LV function at 6 months compared with none in the MRC arm. Serum BNP significantly reduced in the CA group compared with the MRC group (−216 ng/l, p = 0.013). No significant improvement in LVEF, BNP, or other cardiac dimensions was seen in the medical rate control group (Table 3). At 6 months, the presence of sinus rhythm in the CA group was associated with superior rate control compared with the MRC group (−17 beats/min, p = 0.002).

TABLE 2 Change From Baseline in Each Treatment Arm

	Baseline	6 Months	p Value
Catheter ablation (n = 18)			
Cardiac MRI parameters			
LVEF (MRI)	33.0 ± 8.0	47.0 ± 11.3	<0.0001
Myocardial T1 time (ms)	1286 ± 120	1192 ± 77.1	0.00892
LVESV (ml/m^2)	80.4 ± 75.1	63.1 ± 34.3	0.00191
LVEDV (ml/m^2)	118 ± 43.8	113 ± 37.1	0.32
LA volume (ml/m^2)	53.6 ± 15.6	44.9 ± 10.5	0.02626
LV stroke volume (ml/m^2)	37.6 ± 13.9	50.2 ± 10.1	<0.0001
Other parameters			
NYHA functional class	2.56 ± 0.51	1.33 ± 0.49	<0.0001
BNP (ng/l)	321 ± 191	108 ± 74.7	<0.0001
6MWT distance (m)	490 ± 109	536 ± 67.8	0.01943
SF-36 Physical component scores	37.9 ± 10.7	47.7 ± 9.2	0.00023
SF-36 Mental component scores	46.5 ± 10.2	53.8 ± 6.8	0.00122
Medical rate control (n = 18)			
Cardiac MRI parameters			
LVEF (MRI)	35.6 ± 8.2	37.1 ± 7.6	0.45
Myocardial T1 time (ms)	1,224 ± 125	1,255 ± 295	0.44
LVESV (ml/m^2)	75.1 ± 29.4	70.0 ± 27.8	0.31
LVEDV (ml/m^2)	114 ± 36.4	110 ± 33.7	0.51
LA volume (ml/m^2)	52.7 ± 21.4	51.2 ± 13.5	0.73
LV stroke volume (ml/m^2)	39.4 ± 14.4	39.4 ± 10.9	0.99
Other parameters			
NYHA functional class	2.28 ± 0.46	2.00 ± 0.32	0.02045
BNP (ng/l)	210 ± 169	212 ± 176	0.97
6MWT distance	497 ± 128	532 ± 139	0.06
SF-36 Physical component scores	41.8 ± 11.5	44.3 ± 12.3	0.33
SF-36 Mental component scores	50.6 ± 13.2	55.6 ± 15.8	0.11

Values are mean ± SD.

BNP = brain natriuretic peptide; LA = left atrial; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SF-36 = Short Form 36; other abbreviations as in Table 1.

DISCUSSION

This substudy of the CAMERA-MRI trial aimed to determine the recovery of diffuse fibrosis (native T1 mapping) in patients with persistent AF and otherwise unexplained cardiomyopathy who were randomized to CA or MRC and underwent cardiac MRI assessment at baseline and at 6 months. The primary findings were as follows:

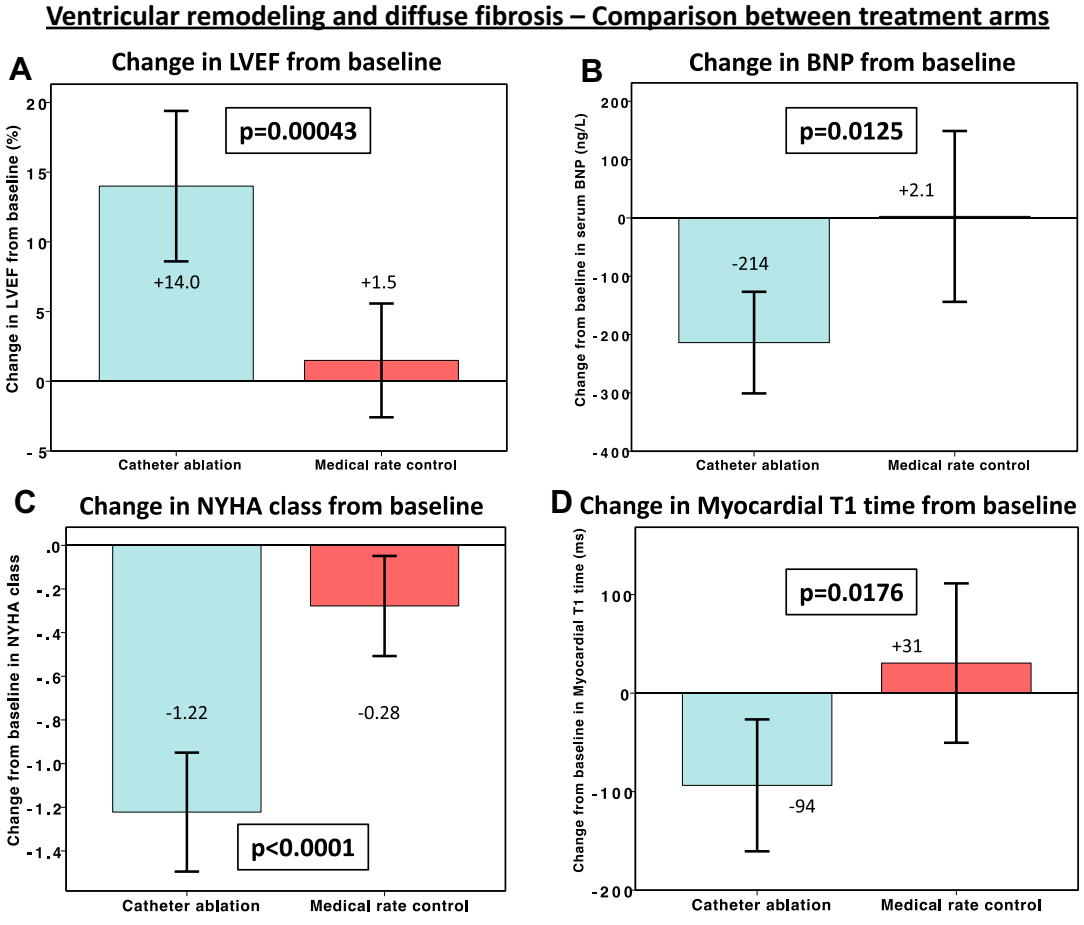
1. There was a regression in diffuse fibrosis in the sinus rhythm group who underwent CA, compared with patients undergoing MRC. In concert with this

TABLE 3 Comparison Between Treatment Arms

	Mean Difference	95% CI	p Value
Cardiac MRI parameters			
LVEF (MRI) (%)	+12.5	5.9 to 19.0	0.00043
Myocardial T1 time (ms)	−124	−23.0 to −225	0.01763
LVESV (ml/m^2)	−12.2	−25.9 to 1.4	0.07
LA volume (ml/m^2)	−8.6	−20.7 to 3.5	0.16
LV stoke volume (ml/m^2)	+12.6	3.7 to 21.5	0.00698
Other parameters			
NYHA functional class	−0.94	−1.29 to −0.60	<0.0001
BNP (ng/l)	−216	−383 to −50.0	0.01245
Average ventricular rate (beats/min)	−16.7	−26.7 to −6.7	0.00176
SF-36 Physical component scores	+7.3	0.7 to 14.0	0.03218

Abbreviations as in Tables 1 and 2.

FIGURE 1 Comparison of 6-Month Outcomes by Treatment Arm



Catheter ablation was associated with **(A)** a significant improvement in LVEF, **(B)** a reduction in serum BNP, and **(C)** a reduction in NYHA functional class. **(D)** This was accompanied by a reduction in myocardial T1 times consistent with a regression of diffuse fibrosis. Bars represent 95% confidence intervals. BNP = brain natriuretic peptide; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

were significant improvements in LVEF, ventricular and atrial chamber dimensions, BNP, and functional capacity.

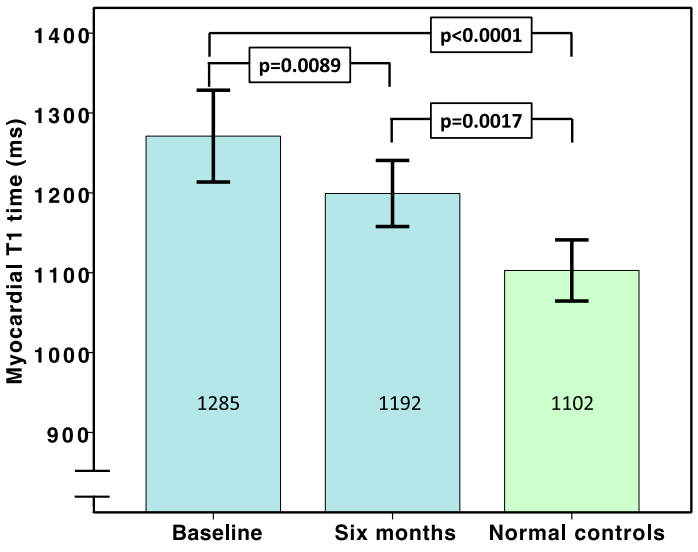
2. Despite regression in diffuse fibrosis, myocardial T1 mapping values in those patients undergoing CA remained higher than those of normal controls without a history of AF.

DIFFUSE FIBROSIS IN IDIOPATHIC CARDIOMYOPATHY AND AF. Quantitative measures of diffuse fibrosis such as extracellular volume calculation and T1 mapping have been validated against collagen content on histology (16–18). In the setting of heart failure, Iles et al. correlated the presence of diffuse fibrosis with reduced systolic function at cardiac biopsy and CMR (3). Other studies have histologically validated the use of native T1 mapping for the detection of diffuse fibrosis in the setting of idiopathic cardiomyopathy (17,19), with a recent study suggesting that native T1 mapping was the most robust approach for assessing diffuse fibrosis in the setting of nonischemic cardiomyopathy (20). Both AF and idiopathic cardiomyopathy have been independently associated with diffuse fibrosis. Ling et al. evaluated the incidence of diffuse ventricular fibrosis using post-contrast T1 mapping in 90 patients (23 controls, 40 with paroxysmal AF, and 27 with persistent AF) and demonstrated an increase in diffuse fibrosis with the presence of AF in a dose-dependent manner. On multivariate analysis, age, AF phenotype, and ejection fraction independently predicted postcontrast T1 time (5). Furthermore, McLellan et al. demonstrated that diffuse fibrosis

independently predicted single-procedure success in patients undergoing CA for AF (4). Elevated T1 times have also been demonstrated with CMR using native T1 in patients referred for AF ablation (21).

REGRESSION OF DIFFUSE FIBROSIS. It is unclear whether diffuse fibrosis, as determined by CMR, in the setting of heart failure is reversible. Several studies have demonstrated that myocardial collagen content, as determined on myocardial biopsy, can be decreased following prolonged angiotensin-converting enzyme inhibition (22) or mineralocorticoid receptor antagonism (23), which was also associated with a reduction in LV chamber stiffness (24). McLellan et al. (2) demonstrated a reduction in myocardial T1 times following successful blood pressure reduction in hypertensive patients undergoing renal denervation. Other studies have longitudinally evaluated diffuse fibrosis in various disease states such as aortic stenosis (25) and acute myocardial infarction (26). The present study prospectively assessed the impact of successful treatment of systolic dysfunction upon diffuse fibrosis with serial CMR. Arrhythmia-mediated cardiomyopathy, when successfully treated with CA, results in significant improvements in ventricular function and reverse cardiac remodeling (8,9,27,28). Because both AF and reduced systolic function may be responsible for diffuse fibrosis, the treatment of both with successful CA affords a unique opportunity to examine the impact of sinus rhythm and reverse remodeling upon diffuse fibrosis. Interestingly, the improvements in T1 times in those both with and without ≥15% improvements in LVEF (−102 ms vs. −83 ms; p = 0.77) suggests that elimination of AF may itself regress fibrosis even in the absence of a large accompanying improvement in LVEF. This may in part explain the reduction in mortality seen with CA in Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation in which the absolute improvement in LVEF was 8% (6). Additionally, a more significant reduction in T1 time was demonstrated in the LGE-positive group because there was a greater initial burden of fibrosis and therefore a greater capacity for reversibility of fibrosis following the restoration of sinus rhythm with CA. The present study demonstrated regression of MRI-detected diffuse fibrosis in concert with the improvement in ventricular function following the restoration of sinus rhythm in arrhythmia-mediated cardiomyopathy. To our knowledge, this is the first time that reversibility of ventricular fibrosis in the setting of systolic dysfunction has been demonstrated in humans on CMR.

FIGURE 2 Myocardial T1 Times in the Catheter Ablation Arm Compared With Normal Controls



Significant improvement is seen from baseline to 6 months; however, T1 times are still significantly higher at 6 months compared with normal controls. **Bars** = 95% confidence intervals.

Nonetheless, at 6 months although improved from baseline, myocardial T1 values remained significantly higher than that of normal controls (p = 0.0017). This may reflect the incomplete recovery of LVEF in the CA group. Alternatively, the mechanisms responsible for diffuse fibrosis may be primarily related to that responsible for the underlying cardiomyopathy rather than being explained by AF alone (the well-recognized "chicken and egg" relationship between AF and heart failure). It is also possible that 6 months may be too short a time to permit complete resolution of diffuse fibrosis. Ling et al. (5) demonstrated that diffuse fibrosis was still detectable despite recovery of LV function at nearly 5 years following successful CA for atrial tachycardia-mediated cardiomyopathy. Animal studies have suggested that the early LV recovery process may be associated with increased collagen deposition (29).

CLINICAL IMPLICATIONS. There are several important clinical implications of these findings. The regression of diffuse fibrosis in concert with

recovery of LV function in patients undergoing successful CA may explain the better-than-expected outcomes with ablation in the AF/heart failure population where procedural success is generally poorer (9,28,30). The reversibility of diffuse fibrosis in the present study presents an opportunity to reduce the precursor to the more permanent form of replacement fibrosis or scar. Early intervention with CA in patients with AF and heart failure may not only reduce interstitial fibrosis but also halt the progression to scar (17). The lack of complete resolution of diffuse fibrosis also has important clinical implications. First, diffuse fibrosis may be a marker of a genetic predisposition to adverse remodeling. The genetic determinants involved in arrhythmia-mediated cardiomyopathy are yet to be determined; however, given that the majority with this common arrhythmia do not develop systolic dysfunction it seems probable that some inherent predisposition may exist (31). Finally, although systolic dysfunction may improve or even normalize, this finding suggests that the ultrastructural aspects of the ventricle may not "normalize" following the restoration of sinus rhythm. Thus, medical treatments for heart failure, such as renin-angiotensin aldosterone and adrenergic system inhibition, should be continued.

STUDY LIMITATIONS. Not all patients enrolled in the CAMERA-MRI trial had sufficient ventricular T1 data both before and after CA because of patient tolerability of the longer scanning time or artifact from the implantable loop recorder. Although used widely in research and academic settings, the clinical utility of T1 mapping in the setting of heart failure has yet to be established. Whether regression of diffuse fibrosis as detected by myocardial T1 mapping translates to a reduction in clinical outcomes (such as hospitalization and cardiac mortality) should be determined by adequately powered prospective studies.

CONCLUSIONS

The improvement in systolic function and reverse ventricular remodeling following successful treatment of AF-mediated cardiomyopathy with CA is accompanied by regression of diffuse fibrosis. This may have important implications for the timely treatment of arrhythmia-mediated cardiomyopathy to minimize irreversible ventricular remodeling.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Both AF and systolic heart failure have been associated with increased diffuse fibrosis as detected by cardiac MRI, using native T1 mapping, which has been histologically validated. The reversibility of this remodeling following successful treatment of both conditions is not known, however. The at least partial regression of diffuse fibrosis in patients with AF-mediated cardiomyopathy suggests that timely intervention by the restoration of sinus rhythm may minimize irreversible ventricular remodeling.

TRANSLATIONAL OUTLOOK: Despite this partial regression of diffuse fibrosis, larger and longer-term studies are needed to determine the impact of these findings on clinical outcomes and the longevity of ventricular recovery.

REFERENCES

1. Ho CY, López B, Coelho-Filho OR, et al. Myocardial fibrosis as an early manifestation of hypertrophic cardiomyopathy. N Engl J Med 2010;363:552–63.

2. McLellan AJ, Schlaich MP, Taylor AJ, et al. Reverse cardiac remodeling after renal denervation: atrial electrophysiologic and structural changes associated with blood pressure lowering. Heart Rhythm 2015;12:982–90.

3. Iles L, Pfluger H, Phrommintikul A, et al. Evaluation of diffuse myocardial fibrosis in heart failure with cardiac magnetic resonance contrast-enhanced T1 mapping. J Am Coll Cardiol 2008;52:1574–80.

4. McLellan AJA, Ling L-H, Azzopardi S, et al. Diffuse ventricular fibrosis measured by T1 mapping on cardiac MRI predicts success of catheter ablation for atrial fibrillation. Circulation 2014;7:834.

5. Ling LH, Kistler PM, Ellims AH, et al. Diffuse ventricular fibrosis in atrial fibrillation: noninvasive evaluation and relationships with aging and systolic dysfunction. J Am Coll Cardiol 2012;60:2402–8.

6. Marrouche NF, Brachmann J, Andresen D, et al. Catheter ablation for atrial fibrillation with heart failure. N Engl J Med 2018;378:417–27.

7. Di Biase L, Mohanty P, Mohanty S, et al. Ablation Versus amiodarone for treatment of persistent atrial fibrillation in patients with congestive heart failure and an implanted device: results from the AATAC Multicenter Randomized Trial. Circulation 2016;133:1637–44.

8. Prabhu S, Taylor AJ, Costello BT, et al. Catheter ablation versus medical rate control in atrial fibrillation and systolic dysfunction: the CAMERA-MRI Study. J Am Coll Cardiol 2017;70:1949–61.

9. Anselmino M, Matta M, D'Ascenzo F, et al. Catheter ablation of atrial fibrillation in patients with left ventricular systolic dysfunction: a

systematic review and meta-analysis. Circ Arrhythm Electrophysiol 2014;7:1011–8.

10. Addison D, Farhad H, Shah RV, et al. Effect of late gadolinium enhancement on the recovery of left ventricular systolic function after pulmonary vein isolation. J Am Heart Assoc 2016;5.

11. Miller CA, Naish JH, Bishop P, et al. Comprehensive validation of cardiovascular magnetic resonance techniques for the assessment of myocardial extracellular volume. Circulation 2013;6:373.

12. Messroghli DR, Moon JC, Ferreira VM, et al. Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2* and extracellular volume: a consensus statement by the Society for Cardiovascular Magnetic Resonance (SCMR) endorsed by the European Association for Cardiovascular Imaging (EACVI). J Cardiovasc Magn Res 2017;19:75.

13. Costello BT, Springer F, Hare JL, et al. SASHA versus ShMOLLI: a comparison of T1 mapping methods in health and dilated cardiomyopathy at 3 T. Int J Cardiovasc Imaging 2017;33:1551–60.

14. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016;37:2893–962.

15. Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. Stat Med 1998;17:873–90.

16. de Meester de Ravenstein C, Bouzin C, Lazam S, et al. Histological validation of measurement of diffuse interstitial myocardial fibrosis by myocardial extravascular volume fraction from Modified Look-Locker imaging (MOLLI) T1 mapping at 3 T. J Cardiovasc Magn Res 2015;17:48.

17. aus dem Siepen F, Buss SJ, Messroghli D, et al. T1 mapping in dilated cardiomyopathy with cardiac magnetic resonance: quantification of diffuse myocardial fibrosis and comparison with endomyocardial biopsy. Eur Heart J Cardiovasc Imaging 2015;16:210–6.

18. Diao KY, Yang ZG, Xu HY, et al. Histologic validation of myocardial fibrosis measured by T1 mapping: a systematic review and meta-analysis. J Cardiovasc Magn Res 2016;18:92.

19. Nakamori S, Dohi K, Ishida M, et al. Native T1 mapping and extracellular volume mapping for the assessment of diffuse myocardial fibrosis in dilated cardiomyopathy. J Am Coll Cardiol Img 2018;11:48–59.

20. Child N, Suna G, Dabir D, et al. Comparison of MOLLI, shMOLLLI, and SASHA in discrimination between health and disease and relationship with histologically derived collagen volume fraction. Eur Heart J Cardiovasc Imaging 2018;19:768–76.

21. Kato S, Foppa M, Roujol S, et al. Left ventricular native T1 time and the risk of atrial fibrillation recurrence after pulmonary vein isolation in patients with paroxysmal atrial fibrillation. Int J Cardiol 2016;203:848–54.

22. Brilla CG, Funck RC, Rupp H. Lisinopril-mediated regression of myocardial fibrosis in patients with hypertensive heart disease. Circulation 2000;102:1388.

23. Izawa H, Murohara T, Nagata K, et al. Mineralocorticoid receptor antagonism ameliorates left ventricular diastolic dysfunction and myocardial fibrosis in mildly symptomatic patients with idiopathic dilated cardiomyopathy: a pilot study. Circulation 2005;112:2940–5.

24. Díez J, Querejeta R, López B, González A, Larman M, Martínez Ubago JL. Losartan-dependent regression of myocardial fibrosis is associated with reduction of left ventricular chamber stiffness in hypertensive patients. Circulation 2002;105:2512.

25. Flett AS, Sado DM, Quarta G, et al. Diffuse myocardial fibrosis in severe aortic stenosis: an equilibrium contrast cardiovascular magnetic resonance study. Eur Heart J Cardiovasc Imaging 2012;13:819–26.

26. Chan W, Duffy SJ, White DA, et al. Acute left ventricular remodeling following myocardial infarction: coupling of regional healing with remote extracellular matrix expansion. J Am Coll Cardiol Img 2012;5:884–93.

27. Hsu L-F, Jaïs P, Sanders P, et al. Catheter ablation for atrial fibrillation in congestive heart failure. N Engl J Med 2004;351:2373–83.

28. Prabhu S, Ling LH, Ullah W, et al. The impact of known heart disease on long-term outcomes of catheter ablation in patients with atrial fibrillation and left ventricular systolic dysfunction: a multicenter international study. J Cardiovasc Electrophysiol 2016;27:281–9.

29. Spinale FG, Zellner JL, Tomita M, Crawford FA, Zile MR. Relation between ventricular and myocyte remodeling with the development and regression of supraventricular tachycardia-induced cardiomyopathy. Circ Res 1991;69:1058.

30. Ullah W, Ling LH, Prabhu S, et al. Catheter ablation of atrial fibrillation in patients with heart failure: impact of maintaining sinus rhythm on heart failure status and long-term rates of stroke and death. Europace 2016;18:679–86.

31. Tsai CT, Lai LP, Kuo KT, et al. Angiotensin II activates signal transducer and activators of transcription 3 via Rac1 in atrial myocytes and fibroblasts: implication for the therapeutic effect of statin in atrial structural remodeling. Circulation 2008;117:344–55.

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